

# Chapter 33

## DIFFERENTIAL DIAGNOSIS AND MANAGEMENT OF FEVER IN TRAUMA

CHRISTIAN POPA, MD\*

---

### INTRODUCTION

### INFECTIOUS CONSIDERATIONS

### NONINFECTIOUS CAUSES OF FEVER

Neurogenic Fever

Drug Fever

Pancreatitis

Acalculous Cholecystitis

Malignant Hyperthermia and Neuroleptic Malignant Syndrome

Serotonin Syndrome

Other Causes

Atelectasis

### WORKUP OF FEVER

### EMPIRIC THERAPY

### TREATMENT OF FEVER

### SUMMARY

*\*Colonel, Medical Corps, US Army; Critical Care Service, Department of Surgery, Walter Reed National Military Medical Center, 8901 Rockville Pike, Bethesda, Maryland 20889*

## INTRODUCTION

Fever is one of the most common physical abnormalities in critically ill patients,<sup>1</sup> and may be caused by infectious or noninfectious etiologies. It is a specific and well-coordinated reaction to a challenge or insult and is part of the systemic inflammatory response. Macrophages and polymorphonuclear leukocytes release endogenous pyrogens such as interleukin-1 that orchestrate a variety of biochemical and physiological responses, of which temperature elevation is only one. Interleukin-1 (and probably other cytokines) stimulates the production of prostaglandins in the fever-mediating region of the preoptic area of the anterior hypothalamus, resulting in fever.<sup>2</sup>

Patients with traumatic injuries have an increased incidence of both fever and infectious complications, resulting in frequent diagnostic workups. A study of 510 critically ill trauma patients found that 79% of patients staying in a surgical and trauma intensive care units (ICUs) for at least 7 days were febrile, and 80% had leukocytosis at some point during their first week of ICU care.<sup>3</sup> A larger retrospective review of 37,448 trauma/neurologic ICU admissions found an overall fever incidence density of 38.2 per 100 days, which was higher than in other surgical, medical, or postcardiac surgery patients.<sup>4</sup> Although the presence of fever always prompts concern about infection, it is recognized that many trauma patients will become febrile despite persistently negative cultures. In these patients, it is thought that the severity of injury frequently leads to increased tissue necrosis, and that the associated stress response causes an increase in granulocytes in the peripheral blood. The increased tissue necrosis and increase in granulocytes lead to subsequent increase in temperature due to the inflammation itself and not necessarily due to an underlying infection.<sup>5</sup>

Surgery, which many trauma patients will undergo, elicits a similar inflammatory response, and both inflammation and macrophage phagocytosis of extravasated blood, common benign postoperative events, have been implicated in a febrile response shortly after surgery.<sup>6</sup> As a result, postoperative fever is a relatively common event immediately after major surgical proce-

dures. A recent prospective observational study of all adult patients (n = 1,032) undergoing inpatient general surgical procedures during a 13-month period at an academic military medical center found an incidence of early postoperative fever (defined as temp >100.4°F in the 72 hours following surgery) of 23.7%.<sup>7</sup>

Multiple studies of critically ill patients have fairly consistently attributed infectious causes to fever in approximately one-half of cases,<sup>8-10</sup> with pneumonia, sinusitis, urinary tract, bloodstream, wound and skin/soft tissue, and intraabdominal infections being frequent etiologies.<sup>11-13</sup> Noninfectious etiologies are responsible for the remaining febrile episodes. These noninfectious causes of fever may include myocardial infarction, cerebrovascular hemorrhage, thrombophlebitis, drug reactions, transfusion reactions, malignant hyperthermia, heat stroke, pancreatitis, and acute adrenal insufficiency.<sup>1,14-18</sup> Because trauma patients are at increased risk for thromboembolic disease, fever in the presence of a new or worsening oxygen requirement and/or persistent tachycardia should also prompt consideration of pulmonary embolism as a possible cause. A review of 311 patients with angiography-proven pulmonary embolism found a 14% incidence of otherwise unexplained fever (usually low grade).<sup>19</sup>

It is important to note that not all patients with infections are febrile. For unclear reasons, approximately 35% of septic patients are normothermic at presentation and another 10% are hypothermic.<sup>20</sup> Septic patients who fail to develop a temperature have a significantly higher mortality than febrile septic patients. Therefore, patients at risk for infection who manifest unexplained hypothermia should be aggressively evaluated.

In summary, although fever often has a noninfectious etiology, the provider must remain vigilant and appropriately evaluate fever when it represents a new finding or a change in the patient's condition. He or she must also employ appropriate empiric or directed antimicrobial therapy along with such proven measures as wound irrigation, removal of infected foreign bodies, debridement of devitalized tissue, and drainage of abscesses.

## INFECTIOUS CONSIDERATIONS

In trauma patients who survive longer than 3 days, infection is second only to severe head injury as the cause of death, and an estimated 37% to 45% of all trauma patients will experience an infectious complication such as pneumonia during their initial hospitalization.<sup>21</sup> Furthermore, there is generalized agreement that war wounds are distinct from civilian traumatic

injuries because high-velocity projectiles and blast devices employed as weapons cause a more severe injury than commonly seen in civilian settings, and the accompanying wounds are frequently contaminated by clothing, soil, and environmental debris.<sup>22</sup> Because of these factors and delay before definitive surgery, war wounds have a higher infection potential compared

to civilian injuries, with an incidence of 3.9% in the first 2 weeks after injury reported in one Vietnam-era study.<sup>23</sup> In addition, military trauma patients often have multiple injuries at multiple sites, allowing multiple avenues for possible infections to occur, so it is not at all infrequent for these patients to be infected at different sites with different organisms simultaneously. Furthermore, the subsequent insertion of various tubes and drains allows easy access of organisms in the intensive care environment into normally sterile sites of these already critically ill patients.<sup>24</sup>

A 2003–2004 survey by Yun et al of infections encountered in combat support hospitals in Iraq<sup>25</sup> found that gram-positive bacteria were responsible for most clinical infections in US troops with coagulase-negative staphylococci, accounting for 34% of isolates, *Staphylococcus aureus* for 26%, and streptococcal species for 11%. In contrast, the 732 cultures obtained from the predominantly Iraqi population yielded mostly gram-negative bacteria: *Klebsiella pneumoniae* (13%), *Acinetobacter calcoaceticus-baumannii* complex (11%), and *Pseudomonas aeruginosa* (10%). Both gram-negative and gram-positive bacteria were resistant to a broad array of antimicrobial agents. A similar retrospective review by Petersen et al of the infection patterns of 211 casualties (of which 85% were Iraqi nationals) evacuated to the USNS *Comfort* from the Iraqi theater during Operation Iraqi Freedom<sup>26</sup> found that 26.5% met criteria for infection. Patients with blast injuries, soft tissue injuries, more than three wound sites, loss of limb, abdominal trauma, and a higher Injury Severity Score (ISS) were more likely to be infected. Most infections involved wounds, which accounted for 84% of cases, followed by bloodstream infections (38%) and positive sputum cultures (21%). *Acinetobacter* infections were most common, representing 36% of all wound and 41% of all bloodstream isolates. *Escherichia coli* and *Pseudomonas* species accounted for 14% each, followed by coagulase-negative staph (9%), *Klebsiella* and *Enterobacter* species (both 6%), and *Proteus* species (5%). The remaining cases represented a mixture of *Streptococcus* species and miscellaneous gram-negative bacteria. Overall, 19% of organisms were gram-positive and 81% were gram-negative. Once again, multidrug resistance was common, with *Acinetobacter* isolates exceeding 80% resistance to all drugs tested except imipenem. *E coli* were 85% resistant to ciprofloxacin, and both *E coli* and *Klebsiella* species were very resistant to third generation cephalosporins. However, all of these isolates were carbapenem susceptible. Similarly pooled data of 66 Operation Iraqi Freedom and Operation Enduring Freedom casualties with orthopedic-related trauma treated at Brooke Army Medical Center in

2006 show that of the 26 patients (40%) who received a course of antibiotics, 13 were treated for *Acinetobacter*, 9 for *Klebsiella* species, 6 for *Pseudomonas aeruginosa*, 5 for *Enterobacter* species, and 6 for methicillin-resistant *S aureus*.<sup>27</sup> This and other data suggest that the pattern of causative organisms is similar in the Iraq and Afghanistan theaters.

In patients with negative cultures and without evidence of war injury-related infection, rare but notable febrile infections that have been reported in soldiers returning from Iraq and Afghanistan include tuberculosis, malaria, Q fever, brucellosis, and leishmaniasis. Tuberculosis is endemic in central and southwest Asia; the World Health Organization estimates a prevalence of 149 cases per 100,000 persons in Afghanistan and 45 cases per 100,000 persons in Iraq in 2011.<sup>28</sup> The overall deployment-associated conversion rate has been estimated at 2.5%.<sup>29</sup> In Iraq, chloroquine-susceptible *Plasmodium vivax* malaria occurs at low rates (150 cases per year in 2008) and there have been no reported cases among US military forces serving there. Conversely, there were 467,123 malaria cases in Afghanistan, as reported to the WHO in 2008.<sup>30</sup> Transmission is seasonal from June to November, with negligible transmission occurring between December and April. Most cases involve *P vivax*, but *P falciparum* is also transmitted.<sup>29</sup> Although soldiers are routinely issued malaria prophylaxis, noncompliance remains a significant issue. An investigation of an outbreak of *P vivax* among Army Rangers after deployment to eastern Afghanistan yielded a self-reported 52% rate of adherence to mefloquine prophylaxis.<sup>31</sup>

Q fever is a zoonotic infection caused by *Coxiella burnetii* usually acquired through inhalation of infected particle aerosols. Infection typically results from direct contact with the reservoir hosts (commonly cattle, goats, and sheep), but it may also occur after exposure to contaminated manure, straw, or dust kicked up by vehicles. Infection presents acutely as either a self-limited febrile (“flu-like”) illness, pneumonia, or hepatitis. Brucellosis, another zoonotic disease endemic to the Middle East, is transmitted to humans through contact with infected animals. *Brucella* bacteria may be ingested, inhaled, or percutaneously inoculated. There are rare reports of brucellosis among deployed US personnel. Visceral leishmaniasis, a protozoan infection usually transmitted by the bite of an infected sand fly, is a form of leishmaniasis that can be asymptomatic, subclinical, or symptomatic and that manifests with chronic fever, pancytopenia, hepatosplenomegaly, and cachexia. In Iraq, visceral leishmaniasis has been mostly reported from the more southern regions, especially among malnourished children.<sup>32</sup>

## NONINFECTIOUS CAUSES OF FEVER

The following are potential noninfectious causes of fever in the ICU patient:

- cerebral infarction/hemorrhage
- adrenal insufficiency
- subarachnoid hemorrhage
- deep venous thrombosis
- postoperative fever (48 h postoperative)
- pulmonary emboli
- posttransfusion fever
- hematoma
- drug fever
- gout/pseudogout
- fat emboli
- cirrhosis (without primary peritonitis)
- myocardial infarction
- gastrointestinal bleeding
- pancreatitis
- phlebitis / thrombophlebitis
- acalculous cholecystitis
- ischemic bowel
- intravenous contrast reaction
- aspiration pneumonitis
- decubitus ulcers
- acute respiratory distress syndrome (both acute and late phases)
- neoplastic fevers
- alcohol or drug withdrawal<sup>20</sup>

While many of these will become evident during the workup due to their presentation, a few deserve additional discussion.

### Neurogenic Fever

Fever after cerebral insult is common, especially when it results in intraventricular hemorrhage, and is independently associated with worse outcomes in patients when compared to nonfebrile similarly injured individuals. Erickson first described neurogenic hyperthermia in patients after brain surgery or head trauma in 1939.<sup>33</sup> Retrospectively studying cohorts of 40 patients, Albrecht et al observed fever of more than 38.0°C in 70% of patients after subarachnoid hemorrhage and in 68% after closed-head injury.<sup>34</sup> Another retrospective review of 251 consecutive patients with spontaneous supratentorial intracerebral hemorrhage admitted to a neurologic critical care unit showed that fever was present in 19% of all patients on admission and occurred in almost all patients (91%) at least once during the first 72 hours after hospitalization.<sup>35</sup> Refractory high fever (> 42°C) in the immediate aftermath of

massive supratentorial<sup>36</sup> or brainstem<sup>37</sup> intracerebral hemorrhage is also well described. The mechanism by which intraventricular hemorrhage may alter hypothalamic function and cause central fever is unknown. Mechanisms proposed include direct hemotoxic damage to thermoregulatory centers in the preoptic region, interference with tonic inhibitory inputs from the lower midbrain that ordinarily suppress thermogenesis, and stimulation of prostaglandin production leading to temperature set-point elevation.<sup>38</sup>

In addition, direct physical or ischemic damage to the baseline temperature control center in the hypothalamus can result in persistent hypothermia or hyperthermia. Patients with such injuries may be hypothermic, with baseline body temperatures as low as 35°C (95°F), or they may be hyperthermic, with baseline temperatures as high as 41.1°C (106°F).<sup>39</sup> Similarly, damage to the hypothalamus can result in inappropriate or uncontrolled intermittent temperature elevations. These patients can have high fevers with relatively minor insults or for no apparent reason.

Hyperthermia of neurologic origin is a diagnosis of exclusion. Patients should be carefully examined and then undergo laboratory testing or imaging to search for a source of infection if indicated. Regardless of etiology, fever should be treated aggressively in head-injured patients because it is independently associated with a poor outcome. Only 1 to 2 degrees of hyperthermia has been shown to be deleterious on outcome in animal models of focal and global ischemia and traumatic brain injury (TBI), and the risk of poor functional outcome is increased with even mild temperature elevation (37.5°C) on admission after ischemic stroke or intracerebral hemorrhage.<sup>40</sup> Initially, sustained fever should be treated with acetaminophen and cooling blankets. Persistent fever that is refractory to acetaminophen and without infectious cause may require adhesive surface-cooling systems and endovascular heat-exchange catheters to maintain normothermia.

### Drug Fever

Although the true incidence of this disorder is unknown, drug fever should also be considered in patients with an otherwise unexplained fever, particularly if they are receiving  $\beta$ -lactam antibiotics, procainamide, or diphenylhydantoin.<sup>41</sup> Any drug can cause fever due to hypersensitivity, and some drugs can also cause fever by inducing phlebitis at the site of administration. Drug fever is usually characterized by high spiking temperatures and shaking chills, lack

of appropriate pulse rate response, and a relative bradycardia in the absence of intrinsic conduction defects or beta-blockade, and may be associated with leukocytosis and eosinophilia. A concomitant maculopapular rash helps establish the diagnosis, but the rash is present in only 5% to 10% of cases. Rarely, an increased white blood cell count with a left shift, eosinophilia, a moderate elevation of serum transaminases, or a markedly elevated erythrocyte sedimentation rate ( $>100$  mm/h) are seen.<sup>42</sup> Fever usually resolves in 1 to 3 days but can take up to 7 days to return to normal after the offending agent is removed.<sup>43</sup>

### Pancreatitis

Pancreatitis should be considered in patients who have suffered trauma to the epigastrium and have phenomena suggestive of intraabdominal injury. Because the blunt force required to injure the pancreas is significant and penetrating trauma usually injures multiple organs, other organs are also affected when the pancreas is injured. Therefore, multiple organ injury is a red flag suggesting the possibility of a pancreatic injury. Trauma to the pancreas can also occur during damage control or elective operative procedures in the upper abdomen and result in pancreatitis postoperatively. Stern reported that the pancreas was injured more often than was recognized during operative procedures and indicated that the pancreas was particularly vulnerable to injury during operations on the gallbladder with exploration of the common duct, splenectomies, right nephrectomies, pancreatic biopsies, and repair of duodenal ulcers.<sup>44</sup> The diagnosis can be confirmed by elevated serum amylase and lipase levels. Although it lacks sensitivity (75% to 92%) and specificity (20% to 60%), measurement of the serum amylase level is the most widely used method of diagnosing pancreatitis. The advantages of amylase testing are that it is quickly performed, easily obtained, and inexpensive. However, a variety of nonpancreatic conditions, notably injury to the salivary glands or bowel, can also cause increased amylase levels. Lipase levels will also be elevated in pancreatitis, and the test has better specificity (50% to 99%) and sensitivity (86% to 100%) than measurement of amylase.<sup>45</sup> Contrast-enhanced computed tomography (CT) scan provides the best imaging of the pancreas and surrounding structures and may be useful when other diagnostic studies are inconclusive. Direct injury as well as retroperitoneal hematoma, retroperitoneal fluid, free abdominal fluid, and pancreatic edema, all of which frequently accompany injuries to the pancreas, can be visualized. Ultrasound may be a suitable alternative in nonobese patients, with a reported sensitivity of 62%

to 95%<sup>45</sup>; however, the pancreas will be obscured by bowel gas in up to 35% of patients.<sup>46</sup>

### Acalculous Cholecystitis

Acalculous cholecystitis, the result of gallbladder ischemia and bile stasis, has an estimated incidence of 1.5% among critically ill patients.<sup>47</sup> It is frequently unrecognized, especially in septic patients or in patients recovering from abdominal sepsis, because of the nonspecific clinical signs (pain in the right upper quadrant, nausea, vomiting, and fever) and laboratory workup (leukocytosis and elevated liver enzymes). A high index of suspicion is needed to prevent delays in diagnosis and subsequent disease progression to ischemia, gangrene, and perforation. Right upper quadrant abdominal ultrasound findings such as a gall bladder wall thickness greater than 3 mm, intramural lucencies, gallbladder distension, pericholecystic fluid, or intramural sludge are suggestive but not specific for acute cholecystitis. CT scanning also has a high sensitivity and specificity for these findings and will better depict an inflammatory pericholecystic reaction in the gallbladder fossa. Hepatobiliary scintigraphy is also a sensitive modality in diagnosing acute cholecystitis but is characterized by a high false-positive rate ( $>50\%$ ) in critically ill patients.<sup>48</sup> The treatment of choice is percutaneous cholecystostomy, which is also the definitive therapy in most patients. Open cholecystectomy is, however, recommended if the abdominal signs, fever, and leucocytosis do not improve within 48 hours of percutaneous cholecystostomy.<sup>20</sup>

### Malignant Hyperthermia and Neuroleptic Malignant Syndrome

Malignant hyperthermia (MH) and neuroleptic malignant syndrome (NMS) are rare but should be considered in the critically ill trauma patient when fever is especially high. MH is more common in the operating room than in the ICU and occurs after general anesthesia with volatile inhalational agents and/or succinylcholine (suxamethonium). It can take up to 24 hours after exposure to an offending agent to manifest. It is caused by a mutation in the ryanodine calcium channel of sarcoplasmic reticulum leading to uncontrolled intracellular calcium release and tonic contraction of skeletal muscle with ensuing hyperthermia, acidosis, rhabdomyolysis, and hyperkalemia.<sup>49</sup> Also typical are tachycardia, increased carbon dioxide production, and elevated creatine phosphokinase (CPK) values consistent with muscle injury. Treatment involves external or internal cooling, correction of acidosis and hyperkalemia, and rapid administration of dantrolene.

NMS is a consequence of blockade of dopamine receptors and is usually caused by antipsychotic agents (phenothiazines, thioxanthenes, butyrophenones). It also manifests with muscle rigidity, high fever, and increasing CPK concentrations. It is similarly treated with discontinuation of the offending agent, cooling, supportive care, and muscle relaxation with benzodiazepines and/or dantrolene. Unlike in MH, because the rigidity and resultant hyperthermia in NMS are centrally initiated, both symptoms can be rapidly controlled with nondepolarizing neuromuscular blockade once the airway is secured.

### Serotonin Syndrome

Serotonin syndrome is another often unrecognized pharmacologic cause of fever encountered in the ICU. It consists of a clinical triad of mental status changes, autonomic hyperactivity, and neuromuscular abnormalities and is caused by overstimulation of central 5-HT<sub>1A</sub> receptors. It always occurs within 24 hours of an increase in dose or addition of a serotonergic agent and is believed to remain unresolved unless the offending agent is discontinued. A variety of serotonergic agents have been implicated in the syndrome, including selective serotonin reuptake inhibitors; tricyclic antidepressants; 5-HT<sub>3</sub> antagonist antiemetics (ondansetron, granisetron); metoclopramide; dextromethorphan; fentanyl; pentazocine; tramadol; buspirone; and trazodone; as well as sumatriptan, linezolid, valproate, lithium, and monoamine oxidase inhibitors. Especially severe reactions have been reported with meperidine. Although most patients recover, rare cases can result in death. Treatment consists of discontinuation of the offending agent and administration of benzodiazepines, which have a beneficial effect in moderate cases. Similar to NMS, in severely ill patients with hyperthermia (a temperature higher than 41.1°C) immediate

paralysis should be induced with nondepolarizing agents such as vecuronium, followed by orotracheal intubation and ventilation.<sup>50</sup> Succinylcholine should be avoided because of the risk of arrhythmia from hyperkalemia associated with rhabdomyolysis. Therapies such as propranolol, bromocriptine, and dantrolene are not recommended.<sup>51</sup>

### Other Causes

Other noninfectious causes of fever in critically ill patients are heatstroke, withdrawal of certain drugs such as alcohol, opiates, barbiturates, or benzodiazepines (often with associated tachycardia, diaphoresis, and hyperreflexia), and blood transfusion (especially platelets). Febrile nonhemolytic transfusion reactions are common and are thought to stem from the formation and/or release of cytokines during the storage of the blood. They are estimated to occur in approximately 3% to 7% of patients receiving red blood cell transfusions and 20% to 30% of those receiving platelet transfusions. On occasion, fevers can approach 40°C (104°F). Also, large isolated hematomas have been reported to result in fever in both adult<sup>52</sup> and pediatric patients.<sup>53</sup>

### Atelectasis

Atelectasis is often attributed as a cause of fever in the ICU but conclusive data to support this is lacking. Inducing atelectasis in experimental animals by ligation of a mainstem bronchus does not produce fever.<sup>54,55</sup> Furthermore, Engoren studied 100 postoperative cardiac surgery patients and was unable to demonstrate a relationship between atelectasis and fever.<sup>56</sup> Currently, the role of atelectasis as a cause of fever is unclear; however, atelectasis probably does not cause fever in the absence of pulmonary infection.<sup>20</sup>

## WORKUP OF FEVER

The workup of the febrile ICU patient should be directed by the history, physical examination findings, and results of initial diagnostic tests. As always, the evaluation should start with a detailed history, which can help the clinician narrow the differential. A detailed geographical history and the time of onset and duration of symptoms are essential for a complete workup. The history should also include details of visits to farms, caves, and health facilities; consumption of local foods and unpurified water; activities involving fresh or salt water exposure; immunizations and travel prophylaxis received (and compliance with the requirements); as well as sexual activity. A history of

contact with ill individuals can be helpful, particularly for localized epidemics (eg, *Legionella*), emerging infections (eg, severe acute respiratory syndrome), or risk assessment for viral hemorrhagic fever.

It is useful to remember that postoperative fever is common within the first 72 hours after surgery. It is usually caused by the release of endogenous pyrogens into the bloodstream, and is usually not of infectious etiology. In these patients, during the first 72 hours and if fever is the only indication, a chest x-ray or cultures are not mandatory, while surgical wounds should be examined daily for infection and a high level of suspicion should be maintained for thromboembolic events

(pulmonary embolism, deep venous thrombosis) or thrombophlebitis.<sup>42</sup> If the patient clinically worsens or remains febrile longer than 72 hours, at which point infection becomes increasingly likely, further investigation is warranted.

Predisposing factors, the type and site of surgery, and underlying comorbidities should be taken into account to help guide the subsequent workup and treatment. The most common infections historically reported in ICU patients are pneumonia, followed by sinusitis, bloodstream infection, and catheter-related infection.<sup>20</sup> Of note, pneumonia is particularly common after upper abdominal surgery or thoracic surgery, wound infections after upper abdominal surgery, and urinary infections after lower abdominal surgery.<sup>57</sup> In all febrile patients, before the initiation of any treatment, at least two blood cultures by separate needles from different sites as well as other appropriate cultures should be obtained.

For patients with fever alone who are otherwise stable, there is usually no need to remove or change all in-dwelling catheters. Patients with worsening sepsis, vasopressor-dependent shock, peripheral embolization, disseminated intravascular coagulation, or acute respiratory distress syndrome should be started on empiric antibiotic therapy after cultures are obtained, and should have all intravascular catheters removed and then reinserted at new sites if indicated.<sup>58</sup> Since up to 20% of central venous catheters are colonized at removal, most unassociated with local infection or bacteremia/fungemia, routine culture of central venous catheters is not recommended. Routine catheter cultures add to microbiology laboratory expense and can lead to unnecessary therapies if interpreted inappropriately. The predictive value of a positive catheter culture is very low when there is a low pretest probability of catheter sepsis, and catheters removed from ICU patients should only be cultured if there is strong clinical suspicion of catheter sepsis.<sup>42</sup>

Although not routinely performed, if the expertise needed for processing is available, quantitative cultures can be drawn from central catheters and peripheral veins if central line infection is strongly suspected and there is no obvious tunnel infection. The diagnosis of line-related sepsis can be made by a colony count in blood cultures drawn from the catheter that is 10 times higher than the colony count in cultures drawn peripherally<sup>59</sup> or by a difference of 2 hours or more in time to positivity between the catheter and peripheral cultures.<sup>60</sup>

In continuous bacteremia, as with endocarditis or intravascular infections, three sets of blood cultures are usually adequate to recover organisms.<sup>61</sup> In addition, a complete metabolic profile including liver function

tests is helpful in determining the etiology. A marked increase in alkaline phosphatase and a rising bilirubin can suggest cholecystitis. Unfortunately, this finding is also nonspecific because increased liver enzymes can also be seen in bacteremia and drug-induced fever, and increases in alkaline phosphatase occur with bony injuries. An elevated lipase likewise can be of diagnostic value and may indicate traumatic or drug-induced pancreatitis.

On urinalysis, pyuria, microscopic hematuria, and positive cultures may point to a diagnosis of urinary tract infection. However, a positive urine culture in catheterized patients is not always indicative of infection, and the diagnosis of urinary tract infection as a source of the fever in these patients should be a diagnosis of exclusion. The presence of sterile pyuria should prompt consideration of tuberculosis as well as a search for eosinophiluria, which would suggest a drug-induced interstitial nephritis.

A chest radiograph should be obtained to rule out pneumonia. The presence of infiltrates can make it difficult to differentiate pneumonia from pulmonary contusions and/or infarct, fluid overload, or even congestive heart failure. It is often necessary to obtain a noncontrast CT scan of the chest, especially in patients who are ventilator dependent. If pleural effusions are present, a thoracentesis may be considered to rule out empyema. Sputum collection for Gram stain and culture can be valuable to guide antibiotic choice when pneumonia is present. Stool testing for *Clostridium difficile* toxin should be done in patients who have received antibiotics in the recent past, even when diarrhea is not a prominent symptom; testing of stool for fecal leukocytes is sensitive but not specific for diagnosing pseudomembranous enterocolitis and infection with enteroinvasive bacteria.

If the initial workup is unrevealing, a CT scan of the abdomen and pelvis, with intravenous contrast when possible, can be done to look for intraabdominal abscess, especially in patients who have undergone penetrating abdominal trauma or abdominal surgery. CT scanning can also reveal a retroperitoneal hematoma, cholecystitis, pancreatitis, or colitis suggestive of pseudomembranous enterocolitis. It is important to note that an abscess will take time to organize and form following abdominal injury or surgery, and a study obtained in the first few days after such an injury or surgery will likely show nonspecific intra-peritoneal fluid collections and/or residual free air that is unlikely to change clinical management or outcome. There is little data in the literature to guide the clinician on the optimal timing of CT scanning to obtain the highest positive yield. A retrospective study of 53 critically ill surgical patients found that no scan

was positive for abscess prior to the 8th postoperative day and recommends not obtaining a CT scan in the 1st week following abdominal surgery in the workup of sepsis.<sup>62</sup> Abdominal ultrasonography can also be considered. This low-cost noninvasive test can be performed at bedside in the unstable patient, and can detect fluid collections as well as abnormalities of the liver, gallbladder and hepatobiliary system, and the pancreas.

### EMPIRIC THERAPY

If an infectious cause of fever is suspected, urgent initiation of empiric antimicrobial therapy is necessary for unstable or high-risk patients while the diagnostic evaluation is ongoing and before culture results are available. Delay of effective antimicrobial therapy is associated with increased mortality from

CT scan of the sinuses without contrast may also be done to look for sinusitis, especially in patients with a nasogastric tube or nasotracheal tubes. Sinusitis occurs in approximately 5% of ICU patients and more frequently in neurosurgical patients.<sup>63</sup> If this approach does not lead to a diagnosis, venous Doppler ultrasonography of the lower extremities and/or a thin-cut CT scan of the chest will help to rule out thromboembolic disease in the right setting.

infection.<sup>64,65</sup> Therefore, antibiotic therapy should begin within 1 hour after the diagnosis of severe sepsis or septic shock is considered.<sup>66</sup> The choice of regimen will depend on the suspected infectious etiology and must be broad enough to cover the likely pathogens.

### TREATMENT OF FEVER

Providers commonly treat fever due to concern that fever may cause patient discomfort and result in undue metabolic stress in unstable critically ill patients with limited reserve. There is widespread agreement that fever in the presence of TBI is associated with worsened neurologic outcomes, including longer ICU stays, increased intracranial pressure, lower Glasgow coma scale scores, and poorer functional status.<sup>67-69</sup> In the presence of TBI, fever may be associated with increased excitatory amino acid release, increased vasogenic edema, increased intracranial pressure, and increased metabolic expenditure, all of which ultimately result in increased neuronal loss.<sup>70</sup> Because of these effects, it is prudent to avoid hyperthermia in TBI patients through use of acetaminophen and external cooling in the absence of contraindications. Drugs that inhibit platelet function are best avoided, however.

Conversely, there is little data in the literature to support the treatment of fever in nonneurologic critically ill patients given that fever is a normal host response to infection. In a randomized study of 38 febrile surgical ICU patients, use of external cooling resulted in no significant differences in recurrence of fever, incidence of infection, antibiotic therapy, length of stay in the ICU and hospital, or mortality.<sup>71</sup> Similarly, Schulman et al conducted an open, random-

ized, prospective clinical trial comparing an aggressive fever treatment strategy (acetaminophen for fever > 38.5°C and a cooling blanket added if > 39.5°C) with a permissive strategy (treatment reserved for fever > 40°C only) in patients without brain injury admitted to a trauma unit. Of note, the study was prematurely stopped due to safety concerns after interim analysis revealed an excess mortality rate of 7 of 44 patients (16%) in the aggressive as compared to 1 of 38 (3%) in the permissive group ( $P = .06$ ).<sup>72</sup> Laupland's retrospective review of 24,204 ICU admissions likewise concluded that the presence of fever was not associated with increased ICU mortality and was actually associated with improved survival among the subset of trauma and neurologic patients.<sup>4</sup> Thus, although fever has some harmful effects, it appears to be an adaptive response that helps rid the host of invading pathogens and has been shown to enhance several parameters of immune function, including antibody production, T-cell activation, production of cytokines, and enhanced neutrophil and macrophage function.<sup>73-75</sup> Therefore, in the absence of patient discomfort, cardiac or pulmonary insufficiency, myocardial ischemia or neurologic injury, and if there is minimal potential or actual patient detriment, fever should be considered a normal physiologic response to inflammation and should not actively be suppressed.

### SUMMARY

In summary, fever is a common finding in critically ill trauma patients, and may be caused by infectious or noninfectious etiologies. The presence of fever in a criti-

cally ill injured patient should prompt a thorough evaluation including a detailed geographic history, physical examination with careful inspection of wounds, and a

search for signs of acute abdomen or occult infections such as sinusitis or perirectal abscess. Blood cultures, chest radiograph, urinalysis, and urine culture should be obtained and will often yield a diagnosis. Unstable or deteriorating patients should be promptly started on empiric antibiotic therapy and should have in-dwelling invasive lines removed or exchanged. Noninfectious

causes of fever should also be considered, especially in patients who appear nontoxic despite recurrent high fevers and a workup that does not reveal an infectious cause. Fever should be aggressively treated in patients with head injuries, although it has not been shown to be detrimental in other groups and may be beneficial for patients battling infection.

## REFERENCES

1. Cunha BA, Shea KW. Fever in the intensive care unit. *Infect Dis Clin North Am*. 1996;10:185–209.
2. Dinarello CA. Thermoregulation and the pathogenesis of fever. *Infect Dis Clin North Am*. 1996;10:433–449.
3. Clardige JA, Golob JF Jr, Leukhardt WH, et al. The “fever workup” and respiratory culture practice in critically ill trauma patients. *J Crit Care*. 2010;25(3):493–500.
4. Laupland KB, Shahpori R, Kirkpatrick AW, Ross T, Gregson DB, Stelfox HT. Occurrence and outcome of fever in critically ill adults. *Crit Care Med*. 2008;36(5):1531–1535.
5. Border JR. Trauma and sepsis. In: Worth MH Jr, ed. *Principles and Practice of Trauma Care*. Baltimore, MD: Williams & Wilkins; 1982: 330–387.
6. Badillo AT, Sarani B, Evans SR. Optimizing the use of blood cultures in the febrile postoperative patient. *J Am Coll Surg*. 2002;194:477–487.
7. Lesperance R, Lehman R, Lesperance K, Cronk D, Martin M. Early postoperative fever and the “routine” fever workup: results of a prospective study. *J Surg Res*. 2011;171:245–250.
8. Circiumaru B, Baldock G, Cohen J. A prospective study of fever in the intensive care unit. *Intensive Care Med*. 1999;25:668–673.
9. Barie PS, Hydo LJ, Eachempati SR. Causes and consequences of fever complicating critical surgical illness. *Surg Infect (Larchmt)*. 2004;5:145–159.
10. Peres Bota D, Lopes Ferreira F, Melot C, Vincent JL. Body temperature alterations in the critically ill. *Intensive Care Med*. 2004;30:811–816.
11. Laupland KB, Gregson DB, Zygun DA, Doig CJ, Mortis G, Church DL. Severe bloodstream infections: a population-based assessment. *Crit Care Med*. 2004;32:992–997.
12. Laupland KB, Zygun DA, Davies HD, et al. Incidence and risk factors for acquiring nosocomial urinary tract infection in the critically ill. *J Crit Care*. 2002;17:50–57.
13. van Zanten AR, Dixon JM, Nipshagen MD, de Bree R, Girbes AR, Polderman KH. Hospital-acquired sinusitis is a common cause of fever of unknown origin in orotracheally intubated critically ill patients. *Crit Care*. 2005;9:R583–590.
14. Hebert PC, Fergusson D, Blajchman MA, et al. Clinical outcomes following institution of the Canadian universal leukoreduction program for red blood cell transfusions. *JAMA*. 2003;289:1941–1949.
15. Bouchama A, Knochel JP. Heat stroke. *N Engl J Med*. 2002;346:978–1988.
16. Oliveira-Filho J, Ezzeddine MA, Segal AZ, et al. Fever in subarachnoid hemorrhage: relationship to vasospasm and outcome. *Neurology*. 2001;56:1299–1304.
17. Chin R. Adrenal crisis. *Crit Care Clin*. 1991;7:23–42.

18. Smego RA Jr, Durack DT. The neuroleptic malignant syndrome. *Arch Intern Med.* 1982;142:1183–1185.
19. Stein PD, Afzal A, Henry JW, Villareal CG. Fever in acute pulmonary embolism. *Chest.* 2000;117:39–42.
20. Marik PE. Fever in the ICU. *Chest.* 2000;117:855–869.
21. Hoover L, Bochicchio GV, Napolitano LM, et al. Systemic inflammatory response syndrome and nosocomial infection in trauma. *J Trauma.* 2006;61(2):310–317.
22. Bellamy R, Zajtcuk R. The management of ballistic wounds of soft tissue. In: Bellamy RF, Zajtcuk R, eds. *Conventional Warfare–Ballistic, Blast and Burn Injuries.* In: Bellamy RF, Zajtcuk R, eds. *Textbooks of Military Medicine.* Washington, DC: Department of the Army, Office of The Surgeon General, Borden Institute; 1991: 163–220.
23. Hardaway RM 3rd. Viet Nam wound analysis. *J Trauma.* 1978;18(9):635–664.
24. Caplan ES, Hoyt NJ. Infection surveillance and control in the severely traumatized patient. *Am J Med.* 1981;70:638–640.
25. Yun HC, Murray CK, Roop SA, Hospenhal DR, Gouridine E, Dooley DP. Bacteria recovered from patients admitted to a deployed U.S. military hospital in Baghdad, Iraq. *Mil Med.* 2006;171:821–825.
26. Petersen K, Riddle MS, Danko JR, et al. Trauma-related infections in battlefield casualties from Iraq. *Ann Surg.* 2007;245:803–811.
27. Murray KC. Epidemiology of infections associated with combat-related injuries in Iraq and Afghanistan. *J Trauma.* 2008;64(3 Suppl):S232–S238.
28. World Health Organization (WHO) estimates of tuberculosis incidence by country, 2011. [http://www.hpa.org.uk/web/HPAweb&HPAwebStandard/HPAweb\\_C/1195733758290](http://www.hpa.org.uk/web/HPAweb&HPAwebStandard/HPAweb_C/1195733758290). Accessed July 10, 2012.
29. Aaronson, NE, Sanders JW, Moran, KA. In harm's way: Infections in deployed American military forces. *Clin Infect Dis.* 2006;43(8):1045–1051.
30. World Health Organization. Malaria, total reported cases. <http://rho.emro.who.int/rhodata/?vid=2694>. Accessed July 4, 2011.
31. Kotwal R, Wenzel RB, Sterling RA, Porter WD, Jordan NN, Petrucci BP. An outbreak of malaria in US Army Rangers returning from Afghanistan. *JAMA.* 2005;293:212–216.
32. World Health Organization. *Communicable Disease Profile: Iraq.* Geneva, Switzerland: World Health Organization; 2003: 42–45.
33. Erickson TC. Neurogenic hyperthermia. *Brain.* 1939;62:172–190.
34. Albrecht RF 2nd, Wass CT, Lanier WL. Occurrence of potentially detrimental temperature alterations in hospitalized patients at risk for brain injury. *Mayo Clin Proc.* 1998;73:629–635.
35. Schwarz S, Hafner K, Aschoff A, Schwab S. Incidence and prognostic significance of fever following intracerebral hemorrhage. *Neurology.* 2000;54(2):354–361.
36. Chin RL, Gelb A. High temperature with cerebral hemorrhage. *Ann Emerg Med.* 1999;34:411.
37. Kitanaka C, Inoh Y, Toyoda T, Sasaki T, Equchi T. Malignant brain stem hyperthermia caused by brain stem hemorrhage. *Stroke.* 1994;25:518–520.
38. Shibata M. Hyperthermia in brain hemorrhage. *Med Hypotheses.* 1998;50:185–190.
39. Lorin MI. Fever in critically ill patients. *Semin Pediatr Infect Dis.* 2000;11(1):13–18.

40. Commichau C, Scarneas N, Mayer SA. Risk factors for fever in the neurologic intensive care unit. *Neurology*. 2003;60(5):837–841.
41. Mackowiak PA, LeMaistre CF. Drug fever: a critical appraisal of conventional concepts. An analysis of 51 episodes in two Dallas hospitals and 97 episodes reported in the English literature. *Ann Intern Med*. 1987;106:728–733.
42. O'Grady N, Barie PS, Bartlett JG, et al. Guidelines for evaluation of new fever in critically ill adult patients: 2008 update from the American College of Critical Care Medicine and the Infectious Diseases Society of America. *Crit Care Med*. 2008;36(4):1330–1349.
43. Cunha BA. Drug fever: the importance of recognition. *Postgrad Med*. 1986;80:123–129.
44. Stern EL. Traumatic injuries to the pancreas. *Am J Surg*. 1930;8:58–74.
45. Munoz A, Katerndahl DA. Diagnosis and management of acute pancreatitis. *Am Fam Physician*. 2000;62:164–174.
46. Gamate VV. Diagnostic tests for acute pancreatitis. *Gastroenterologist*. 1994;2:119–130.
47. Orlando R 3rd, Gleason E, Drezner AD. Acute acalculous cholecystitis in the critically ill patient. *Am J Surg*. 1983;145:472–476.
48. Kalff V, Froelich JW, Lloyd R, et al. Predictive value of an abnormal hepatobiliary scan in patients with severe intercurrent illness. *Radiology*. 1983;146:191–194.
49. Heiman-Patterson TD. Neuroleptic malignant syndrome and malignant hyperthermia: important issues for the medical consultant. *Med Clin North Am*. 1993;77:477–492.
50. Boyer EW, Shannon M. The serotonin syndrome. *N Engl J Med*. 2005;352:1112–1120.
51. Gillman PK. The serotonin syndrome and its treatment. *J Psychopharmacol*. 1999;13:100–109.
52. Chmel H, Palmer JA, Eikman EA. Soft tissue hematoma as a cause of fever in the adult. *Diagn Microbiol Infect Dis*. 1988;11:215–219.
53. Clarke SA, Ehrlich MG, Mankin HJ, Ryan JF, Doppelt Sh. Hematoma-induced febrile response in the pediatric patient. *J Podiatr Orthop*. 1983;39:333.
54. Shields RT Jr. Pathogenesis of postoperative pulmonary atelectasis; an experimental study. *Arch Surg*. 1949;58:489–503.
55. Lansing AM. Mechanism of fever in pulmonary atelectasis. *Arch Surg*. 1963;87:168–174.
56. Engoren M. Lack of association between atelectasis and fever. *Chest*. 1995;107:81–84.
57. Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft-tissues infections. *Clin Infect Dis*. 2005;41:1373–1406.
58. Mayhall CG. Diagnosis and management of infections of implantable devices used for prolonged venous access. *Curr Clin Top Infect Dis*. 1992;12:83–110.
59. Fan ST, Teoh-Chan CH, Lau KF. Evaluation of central venous catheter sepsis by differential quantitative blood culture. *Eur J Clin Microbiol Infect Dis*. 1989;8:142–144.
60. Raad I, Hanna HA, Alakech B, Chatzinikolaou I, Johnson MM, Tarrand J. Differential time to positivity: a useful method for diagnosing catheter-related bloodstream infections. *Ann Intern Med*. 2004;140:18–25.
61. Fefer P, Raveh D, Rudensky B, Schlesinger Y, Yinnon AM. Changing epidemiology of infective endocarditis: a retrospective survey of 108 cases, 1990–1999. *Eur J Clin Microbiol Infect Dis*. 2002;21:432–437.

62. Norwood SH, Civetta JM. Abdominal CT scanning in critically ill surgical patients. *Ann Surg.* 1985;202(2):166–175.
63. Laws C, Jallo J. Fever and infection in the neurosurgical intensive care unit. *JHN J.* 2010;5(2):23–27.
64. Carnacho-Montero J, Garcia-Garmendia JL, Barrero-Almodovar A, Jimenez-Jimenez FJ, Perez-Paredes C, Ortiz-Leyba C. Impact of adequate empirical antibiotic therapy on the outcome of patients admitted to the intensive care unit with sepsis. *Crit Care Med.* 2003;31:2742–2751.
65. Harbarth S, Garbino J, Pugin J, Romand JA, Lew D, Pittet D. Inappropriate initial antimicrobial therapy and its effect on survival in a clinical trial of immunomodulating therapy for severe sepsis. *Am J Med.* 2003;115:529–535.
66. Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med.* 2008;36(1):296–327.
67. Jiang JY, Gao GY, Li WP, Yu MK, Zhu C. Early indicators of prognosis in 846 cases of severe traumatic brain injury. *J Neurotrauma.* 2002;19:869–874.
68. Stocchetti N, Rossi S, Zanier ER, Colombo A, Beretta L, Citerio G. Pyrexia in head-injured patients admitted to intensive care. *Intensive Care Med.* 2002;28:1555–1562.
69. Diring MN, Reaven NL, Funk SE, Uman GC. Elevated body temperature independently contributes to increased length of stay in neurologic intensive care unit patients. *Critical Care Med.* 2004;32:1489–1495.
70. Thompson HJ, Tkacs NC, Saatman KE, Raghupathi R, McIntosh TK. Hyperthermia following traumatic brain injury: a critical evaluation. *Neurobiol Dis.* 2003;12:163–173.
71. Gozzoli V, Schottker P, Suter PM, et al: Is it worth treating fever in intensive care unit patients? Preliminary results from a randomized trial of the effect of external cooling. *Arch Intern Med.* 2001;161:121–123.
72. Schulman CI, Namias N, Doherty J, et al. The effect of antipyretic therapy upon outcomes in critically ill patients: a randomized, prospective study. *Surg Infect (Larchmt).* 2005;6:369–375.
73. Jampel HD, Duff GW, Gershon RK, Atkins E, Durum SK. Fever and immunoregulation: III. Hyperthermia augments the primary in vitro humoral immune response. *J Exp Med.* 1983;157:1229–1238.
74. van Oss CJ, Absolom DR, Moore LL, Park BH, Humbert JR. Effect of temperature on the chemotaxis, phagocytic engulfment, digestion and O<sub>2</sub> consumption of human polymorphonuclear leukocytes. *J Reticuloendothel Soc.* 1980;27:561–565.
75. Biggar WD, Bohn DJ, Kent G, Barker C, Hamilton G. Neutrophil migration in vitro and in vivo during hypothermia. *Infect Immunol.* 1984;46:857–859.